ESSAY.

THE

SIOLOGICAL EFFECTS

AND

THERAPEUTICAL USES

OF

OPIA AND ITS SALTS.

BY

ROBERTS BARTHOLOW. M.D.,

OF OHIO.

Reperti deinde jam remediis, homines de rationibus eorum disserere coepisse; nec post rationem, medicinam esse inventam; sed post inventam medicinam, rationem esse quaesitam.

CELSUS, Lib. I.

EXTRACTED FROM THE

ACTIONS OF THE AMERICAN MEDICAL ASSOCIATION.

PHILADELPHIA:
INS, PRINTER, 705 JAYNE STREET.
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PRIZE ESSAY.

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La méthode expérimentale, considérée en elle-même, n'est rien autre chose qu'un *raisonnement* à l'aide duquel nous soumettons méthodique nos idées à l'expérience des *faits*.

BERNARD, *Introduction à l'Etude de la Médecine Expérimentale.*

PRIZE ESSAY.

THE

PHYSIOLOGICAL EFFECTS AND THERAPEUTICAL USES OF ATROPIA AND ITS SALTS.

SCHEME.

In the following pages I have endeavored to ascertain whether our present notions are well-founded in regard to the physiological effects and therapeutical uses of Atropia, and have attempted to add something to the existing stock of knowledge on these subjects. Further, it seemed to me desirable to study the mutual reactions which obtain between atropia and those remedial agents which have properties apparently physiologically antagonistic. Accordingly, after an examination of the physiological effects of atropia, I have extended my researches to include the effects of atropia and physostigmia; of atropia and morphia; of atropia and strychnia; and of atropia and prussic acid. In executing such a design, it is, of course, unnecessary for the investigator to examine subjects no longer involved in doubt. Whenever I have come to points about which differences of opinion exist, or in respect to which it may be desirable to have some further information, I have undertaken the task of examining them anew. It may happen in this way that I pass over ground already explored. The points in which I agree with those who have preceded me, will, therefore, seem to have received additional support. When I have diverged from the settled beliefs, my opinions will appear to be well-founded or not, according to the strength and consistency of the facts adduced in support of them.

My plan includes, also, a study of atropia as a therapeutic agent The ultimate object of all inquiry into the action of remedies is to

increase the means of cure. Moreover, the results of the experimental and clinical methods should be compared, in order to correct the errors of each. We may justly distrust observations based solely upon one of these methods of inquiry. Results obtained by experiments upon animals may be judged insufficient to interpret phenomena as observed in man; clinical observations may be considered unreliable because of the great and constant danger of confounding the *post hoc* with the *propter hoc*. When, however, the facts of both methods agree, we can hardly refuse to accept the conclusions to which they conduct us.

PART I.

EXPERIMENTAL INQUIRY.

CHAPTER I.

PHYSIOLOGICAL EFFECTS OF ATROPIA.

It will save space to admit, that atropia is absorbed into the blood, and through this medium comes to affect remote parts. All authorities are agreed upon this point. It will be convenient to assume, also, what will hereafter be proved, that atropia has a selective action upon certain tissues, that it modifies in a peculiar way the vital endowments of these tissues, evoking phenomena which are characteristic. The symptoms which it produces belong to the nervous system. We may, therefore, assume further, that atropia has a special affinity, so to speak, for nervous tissue. It does not remain long in contact with this tissue, nor combine with it, but having modified its functional acts, passes quickly out of the organism. That, locally applied, it acts upon nervous tissue, we have the proof in the pallor and anæmia which result when a concentrated solution is brushed over a mucous surface; in the dilatation of the pupil, when a solution is dropped into the eye; in the arrest of pain in a part, when it is used over the affected nerves. Learning these facts, we are ready to believe that atropia introduced into the blood, by virtue of an elective affinity—to borrow a term from the chemists—applies itself to nervous tissue.

It is the purpose of this experimental inquiry to ascertain the truth of these assumptions, and to learn what is the real nature of those dynamical changes exerted by atropia on those tissues of the body especially affected by it. In order to accomplish this design it is necessary to commence with the

Effects of Atropia on the Nervous System.[1]—The frog is the most

[1] I have in this inquiry imitated the methods of investigation pursued by Bernard, in his study of the action of the opium alkaloids, and, also, in his *Leçons sur la Physiologie et la Pathologie du Système Nerveux.*

suitable animal for experiments, in studying the actions of remedial agents on the nervous system. In this animal the different parts of the nervous system may be readily examined, and the influence of agents upon them leisurely determined, with almost mathematical accuracy.[1]

In order to a satisfactory determination of the action of atropia on the nervous system, we must first ascertain what influence it has upon the irritability of muscle.

Experiment.—Injected under the skin of the back of a frog a solution containing $\frac{1}{4}$ grain of sulphate of atropia. The first effect observed, was a disorder of muscular movements. In jumping he rose to a considerable height, but fell upon his side. His hind extremities could not be controlled, but sprawled out. These defects of co-ordination were succeeded in a short time by paralysis. The hind extremities became limp, and although he manifested uneasiness when an irritant was applied, was unable to remove them from the source of irritation. The forearms were doubled up under the body, and he manifested a tendency to roll upon the side. An electrical current and mechanical irritants applied to the sciatic produced no contraction of the muscles (gastrocnemius). Direct irritation at first produced muscular contractions, but the muscular irritability was finally lost. The chest was then opened by dividing the sternum, and the heart's action studied. The pulsations of the heart were sixty-two. The apex had a more forward direction, and the ventricular contraction seemed more powerful than is usually observed under these conditions, without the administration of atropia.

In this experiment we perceive that frogs are susceptible to the action of atropia. Co-ordination of the muscles to execute a given movement is first disturbed then destroyed. Next we observe motor paralysis and then sensory paralysis, the muscular irritability being last to disappear. It is necessary, however, to ascertain with more particularity the relation of these phenomena to each other.

[1] Mais s'il fallait tenir compte des services rendus à la science, la grenouille mériterait la première place. Aucun animal n'a servi à faire de plus grandes et de plus nombreuses découvertes sur tous les points de la science, et encore aujourd'hui, sans la grenouille, la physiologie serait impossible. Si la grenouille est, comme on l'a dit, le Job de la physiologie, c'est-a-dire l'animal le plus maltraité par l'expérimentateur, elle est l'animal qui, sans contredit, s'est associé le plus directement a ses travaux et à sa gloire scientifique.—Bernard, *Introduction à l'Etude de la Médecine Expérimentale*, p. 201. Paris, 1865. J. B. Baillière et Fils.

Experiment.—To determine whether the irritability of muscle, or the excitability of nerves is destroyed, inject as before one-fourth of a grain of atropia. When a perfectly flaccid condition of the muscles of the inferior extremities has been produced, isolate the lumbar nerves and apply irritants to them. No contractions of the muscles follow. A galvanic current applied to the gastrocnemius itself, cannot induce its contraction. I find, however, on repeating this experiment, that at an earlier period before complete paralysis is produced, galvanic stimulation applied to the muscle will cause feeble contractions.

It is evident from these experiments that atropia destroys the excitability of nerves and the irritability of muscle, but the loss of muscular irritability takes place, only, after complete paralysis. Lemattre,[1] who has performed this experiment, states in his "conclusion" that the muscular irritability is not entirely destroyed; but, as I have above shown, the result will depend upon the time at which the galvanic irritation is applied to the muscle.

In experiment first, the motor excitability seemed to end before the sensory. Botkin[2] of St. Petersburg who has examined this point, asserts that such is really the result. On the other hand, Lemattre, in his "conclusion," states that the motor excitability survives the sensory. In order to determine this point, it is necessary before bringing the animal under the influence of atropia, to isolate a group of muscles from the blood supply, whilst maintaining the nervous connection. This may be done, by including in a ligature all of the thigh except the sciatic nerve. When the effects of atropia manifest themselves by paralysis of the limbs not embraced in the ligature, an irritant applied to one of the fore extremities will induce reflex contractions in the muscles of the ligatured limb. When this effect can no longer be produced—showing loss of the excitability of the sensory nerves—a galvanic current applied to the sciatic of the ligatured limb will induce contractions of the muscles of this limb—showing that the motor excitability survives the sensory. Such are the details of an experiment performed by Lemattre to solve this problem. Repeating this experiment I was conducted to precisely the same conclusion.

These observations are opposed to the statements of Prof. A. Von Bezold and Dr. Fried. Blœbaum,[3] who have investigated the

[1] Archives Générales de Médecine, Juillet, 1865, p. 49.

[2] Sydenham Society Year Book, 1862.

[3] Journal of Anatomy and Physiology, May, 1868. American Journal of the Medical Sciences, July, 1868.

actions of the sulphate of atropia. These observers affirm that atropia does not affect the muscular irritability, but that it destroys the irritability of the peripheral terminations of the motor nerves. Their conclusions with regard to its action on the sensory nerves are the same as those of Lemattre, which I have confirmed by my own investigations.

Since atropia produces, as I have above shown, paralysis of motor and sensory nerves, it may be presumed to exert this action on the pneumogastric. As this nerve is now generally considered to be the inhibitor or regulator nerve of the heart and lungs, the action of atropia in increasing the action of these organs may be ascribed to the paralyzing action of this agent on the pneumogastric. This is the view taken by Dr. Meuriot,[1] who thinks that the increased action of the heart is due to paralysis of the terminal filaments of the pneumogastric. Lemattre, who has experimentally examined this question, finds that notwithstanding division of the pneumogastric, atropia still increases the action of the heart. It must therefore act as a stimulant to the nervous system of organic life. Meuriot admits that atropia may have an exciting action upon the sympathetic. Dr. John Harley, Physician to King's College Hospital, who has recently[2] investigated the physiological effects of atropia by experiments on man, the horse, and the dog, concludes that this agent exerts a powerful stimulant action on the heart. The experiment of Lemattre proves that this effect is not produced by paralysis of the terminal filaments of the pneumogastric; it must be due, then, to the stimulant effect upon the organic nervous system.

The character of the action of atropia on the sympathetic system may be studied by an examination of its influence over the circulation in the digital membrane of a frog. In making this observation, precautions must be used to avoid error. It is difficult, if not impossible, to make a satisfactory examination of the circulation in the digital membrane without previous division of the medulla, as recommended by Flint.[3]

Experiment.—The digital membrane being stretched, moistened with distilled water and covered with thin glass, is brought in the focus of the instrument. One vessel is kept in view and its diameter measured by an eye-piece micrometer. One fourth of a grain of the sulphate of atropia is then injected under the skin. In

[1] Gazette Hebdomadaire. Ranking's Abstract, July, 1868.

[2] Gulstonian Lectures. Medical Times and Gazette, March, 1868.

[3] The Philosophy of Man, vol. i. p. 285.

less than a minute there occurs considerable perturbation in the movements of the corpuscles, and they pass through the vessel with increased rapidity. No change can be discovered in their form, refraction of light, or other physical qualities. A slight diminution in the calibre of the vessel under examination is observed, but this disappears after some hours, and an evident relaxation of the capillary wall and dilatation of the vessel then take place.

This experiment accords in its results, in part, with a similar one detailed by Lemattre; but this observer does not allude to the relaxation of the vessels which succeeds to the contraction. I have been unable to verify the observation of Lemattre: that application of a solution of atropia to the interdigital membrane caused a diminution in the calibre of the vessels. Meuriot has, however, observed this, as also the relaxation which succeeds to the contraction of the capillaries.

Experiment.—To determine the action of atropia on the heart. Expose the heart of a frog by dividing the sternum and opening sac of pericardium; pulsations 40 per minute. Inject one-fourth of a grain of atropia; pulsations rise in a few minutes to 52, and the contractions of the heart are increased in power. At the end of five hours, pulsations 30, but very feeble.

Experiment.—Expose the heart as in previous experiment. Apply a concentrated solution of atropia, by means of a pipette, through a small opening in the pericardium. Action rapidly diminished in power and frequency, and irritability of muscle finally destroyed.

To give more completeness to these investigations, I have applied the "graphic method" to determine the action of atropia on the heart and arteries of man. It is obvious, that if the statements herein made, in regard to the effects of atropia upon the organic nervous system are not erroneous, the sphygmograph should afford some evidence of their correctness. I do not underrate the difficulties of making reliable observations with this instrument. As Dr. Ainstie[1] has remarked in his review of Dr. Brunton's work "On Digitalis"—"sphygmographic observations by partially skilled hands are in danger of becoming a very serious mischief, as leading to all manner of fallacious conclusions."

In reporting observations made on the sphygmograph, two methods may be pursued: merely to state in general terms the conclusions to which the observer has been conducted; to give the

[1] The Practitioner, Oct. 1868.

observations themselves so that the reader may form his own conclusions in regard to the correctness of the observations and to the proper interpretation to be given them. In using my own instruments,[1] I have attempted to avoid some of the sources of fallacy, by a careful study of the proper method of manipulating it, and I avoid misleading the reader by placing the tracings themselves before him.

A private pupil, Mr. ——, animated by an eminently scientific zeal, submitted himself to a course of experiment. In order to have a standard of comparison, I made observations before the administration of atropia. Time of observation, 6.30 P. M. Pulse, 71. Subjoined is the tracing, taken before atropia was administered:—

No. 1.

The next observation was made five minutes after $\frac{1}{4}\frac{1}{8}$ of a grain of the sulphate of atropia had been injected into the arm. In

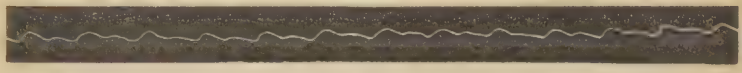
No. 2.

fifteen minutes the pulse had risen to 98, and the tracing was as follows:—

No. 3.

No. 4 represents the tracing at the end of 20 minutes; the pulse

No. 4.



then being 112. At the end of a half-hour the pulse had risen to 120, when the tracing was as follows:—

No. 5.

[1] Sphygmographe de Marey. Margaine, Constructeur, Paris.

The first effect of the atropia as exhibited by the sphygmograph, is to increase the amplitude of the pulse wave, to diminish the arterial tension, and to lower the action of the heart. But these effects are of short duration. The other tracings exhibit a more rapid movement of the heart, and increased tension of the arteries. This increased tension is shown in the ascension, summit and declension of the wave, but especially in the diminished intensity of the dicrotism.

Closely connected with this branch of the subject is the influence of atropia on the animal temperature. Dr. John Harley[1] has noted an elevation of 1° F. externally in man, after the subcutaneous injection of atropia. I have made observations on warm-blooded animals and on man, which are confirmatory of the statements of Dr. Harley. The rise of temperature, 5° to 1° F., is greater on the external than in the internal parts, where the increase is rarely more than 5° F. This rise in temperature does not occur in a regular ratio with the increased pulsations of the heart, as is the case in the normal evolution of fever, where an increase of ten beats of the heart is equal to a rise of 1° F. in temperature. The explanation of Dr. Harley, who attributes the increased body heat to the increased action of the heart, is probably a true one, in a restricted sense. The capillaries are congested because an increased amount of blood is pumped into them by the heart, and the circulation in the capillaries under these circumstances is somewhat impeded, in consequence of the increased tension of the walls of these vessels. In some temperaments this determination to the capillaries is manifest by a more or less intense redness, which is sometimes called a "rash." This heightened color—for it strongly resembles the ruddy hue of youth or the sudden injection of the countenance in blushing—is not an eruption upon the skin. It is a phenomenon identical in character with the redness of the fauces, one of the most constant symptoms produced by the use of atropine. Females having a light complexion are especially liable to this suffusion of the face whether the agent be administered internally, or injected under the skin. The redness is accompanied by a subjective sensation of heat and burning, and there is found to be, on applying a thermometer, a positive increase in temperature.

The midriasis of atropia is another phenomenon pertaining to

[1] Medical Times and Gazette, March 21, 1868, p. 325.

the action of this agent upon the nervous system. By a merely local action, atropia instilled into the eye dilates the pupil and deranges accommodation. It is obvious that this action can be accomplished through two modes only; by a local impression on the muscular tissue or on the nerves supplying the muscles. The iris having a set of radiating, and also a set of circular fibres (the sphincter muscle) innervated, the first by the sympathetic, and the second by the motor oculi; if the action of atropia were exerted on the muscles, dilatation of the pupil would not be produced, for we have no right to assume that one set of fibres would be affected in one way, and another set having the same structure be affected in another way. Irritation of the third pair (motor oculi) produces contraction of the pupil; irritation of the sympathetic produces dilatation of the pupil. Paralysis of the third pair, and hence loss of innervation of circular fibres or sphincter muscle, is followed by a dilated and motionless pupil, the action of the radiating fibres not being opposed by the circular fibres. "Most decisive," says Donders,[1] "however, are the cases of complete paralysis, because they show that this nerve (the third) is the condition, *sine quâ non*, both for reflex and accommodative movement of the pupil, and for the accommodation itself; no trace thereof remains when its paralysis is complete." The local action of atropia then is exerted on the filaments of the third and the sympathetic, just as, introduced into the blood, it has a selective action on these parts of the nervous system. It acts as a paralyzer to the third pair, and as a stimulant to the sympathetic. "The proof consists in the fact, as Ruete was the first to show, that, in complete paralysis of the oculo-motor nerve, the size of the pupil is still considerably increased by atropia; additional dilatation also occurs under atropia after the removal of the nerve in question in animals."[2] Lemattre,[3] who has elaborately examined this question, comes to this conclusion:—

"The midriasis of belladonna is not due to a paralysis, but to a muscular contraction, affecting the radiating and the vaso-motor fibres of the iris."

He rejects the opinion that paralysis of the motor oculi has anything to do with the dilatation of the pupil as produced by atropia.

The eye affected by atropia is presbyopic. This disorder of

[1] On the Anomalies of Accommodation and Refraction of the Eye. Syd. Soc. Edition, p. 578.

[2] Donders, op. cit., p. 589.

[3] Supra, p. 62.

accommodation is differently explained by different observers. According to Graefe,[1] this effect is due to the action of atropia on the radiating fibres of the muscle of accommodation; the contraction of these diminishing the curvature of the crystalline lens and thus rendering the patient presbyopic.

Beside these effects of atropia on the radiating fibres of the iris and of the muscle of accommodation, vision is affected by it, independently of these two modes. Dilatation of the pupil renders the image on the retina blurred and indistinct; sharpness of definition is prevented by the entrance of the most refracted rays. Congestion of the retina itself interferes with the formation of the image. The first effect of atropia is to diminish the calibre of the arterioles, but as I have observed—and this observation is confirmed by Meuriot—the walls of these vessels afterward relax, permitting an increased reflux of blood. This takes place in the tunics of the eye, especially the retina, and may be observed in animals poisoned by atropia, and in man after the use of excessive doses.

The action of atropia on the sympathetic system is further exhibited in its power to promote peristaltic movements, and in the irritability of the bladder produced by ordinary medicinal doses. The former effect is chiefly therapeutical; the latter, however, is a frequent result of the physiological action of atropia. Dr. Fuller,[2] in a paper entitled "On the Administration of Belladonna and on certain Causes which modify its Action," based on observations made on twelve female children from 8 to 19 years of age, noted some difficulty in voiding urine in one case only. But children are remarkably insusceptible to the action of belladonna. My own observations show that the susceptibility to the action of atropia increases with age, and this remark is especially true of the action upon the bladder. Lemattre considers dysuria a common symptom, but especially paralysis of the bladder which he has observed many times. Meuriot[3] notes vesical tenesmus as a constant symptom after the use of large doses. The most constant vesical trouble which has happened under my observation, is a slowness and difficulty of emission. The power of the will over the sphincter has seemed to be obstructed. This may be readily comprehended by a moment's reflection upon the functions of the sphincter mus-

[1] Schmidt's Jahrbücher, Band cxii. 1861.

[2] Medico-Chirurgical Transactions, vol. xlii. p. 289 et seq.

[3] Schmidt's Jahrbücher, Band 139. Jahrgang, 1868, No. 9, p. 284.

cle. It is partly voluntary, partly involuntary in function. The atropia I conceive to act upon the involuntary portion of this sphincter, causing it to contract and thus opposing the action of the will, or at least the consensual action of the voluntary and involuntary portions. In addition to this difficulty, which occurs in almost all cases in which the physiological effects of atropia have been induced, some dysury is produced by the dryness of the vesical and urethral mucous membrane.

The brain is but little affected by an ordinary medicinal dose of atropia. Frontal headache, fulness of the head, and giddiness, are commonly experienced. Toxic doses produce much more serious and characteristic phenomena, but I reserve the consideration of them for another part of this paper.

Secondary Effects of Atropia.—By this phrase I mean to indicate those effects of atropia which are the result of, and consecutive to, its primary action on the nervous system.

Atropia produces dryness of the skin, dryness of the mucous surfaces, and increases the flow of urine. According to Harley, it influences the secondary assimilation, promoting oxidation and the retrograde metamorphosis of tissue. The earliest symptom occurring after hypodermic injection is dryness of the lips and mouth. This extends to the fauces and larynx, producing dysphagia and aphonia in extreme cases. What is the mechanism of this arrest of secretion?

Pflüger[1] has attempted to show that there is a connection between the nerves and the nuclei of the secretory cells of the salivary glands. If this be the case, the secretion would seem to be due to immediate excitation of the gland cells and not through the agency of the vaso-motor nerves by regulating the supply of blood. V. Wittich[2] has shown that the sympathetic directly excites the secretion of the parotid, not by regulating the blood supply passing through this gland, for the influence on its secretion is the same when the flow of blood is stopped. Provost,[3] who has studied the anatomy and physiology of the spheno-palatine ganglion, has shown that avulsion of this ganglion is followed by greatly increased secretion of the Schneiderian mucous membrane. There can be no doubt, then, about the *direct* influence of the sympathetic over secretion; but the precise nature of this influence is not well

[1] Syd. Soc. Biennial Retrospect, 1867. [2] Ibid.
[3] Archiv. de Physiologie, Normale et Path. i. 7-21, and ii. pp. 207-232, 1868.

understood. When, after the administration of atropia, the fauces are injected and the face burns, the temperature being actually elevated, there is greatly diminished secretion notwithstanding the increased amount of blood in the capillaries. This result must then be produced by the action of atropia on those filaments distributed to the secreting gland cells and not merely upon the vaso-motor fibres.

The diuretic effect of atropia has been shown by Meuriot and by Harley, and has been frequently observed clinically by myself. This agent seeks an outlet through the kidneys. Congestion of the Malpighian tufts is due to its presence and to the increased arterial pressure.

The effect which Harley has noted of atropia in increasing the rate of oxidation is a secondary effect due to the increased afflux of blood into the capillaries.

Physiological Effects of Atropia as produced in Man by the Subcutaneous Injection of a Medicinal Dose—$\frac{1}{48}$ of a grain.—Locally there occurs some redness extending for a short distance around the seat of puncture, and a sensation compounded of smarting and itching. In five minutes the influence of the agent upon the action of the heart may be noted, the pulsations becoming a little slower and decidedly fuller and stronger. A bluish-white appearance of the under lip and dryness of the mouth are next experienced; then fulness of the head or a sensation of lightness, tinnitus aurium, giddiness and vertigo. The pupils begin to dilate when the dryness of the lips occurs, but do not reach their maximum dilatation until the lapse of about one hour. As the pupil dilates, the pulse quickens, rising, when the maximum effect is reached, to double or more the normal number per minute. Flushing of the face, injection of the conjunctiva, and slight dimness of vision are then experienced. Movements in walking become somewhat disorderly, owing to the vertigo, and to altered sensibility of the extremities. The dryness of the mucous membrane increases, producing dysphagia, aphonia, and difficult micturition. The urine is voided slowly and with some straining. Nausea and vomiting are apt to occur as the influence of the atropia declines. Some relaxation of the bowels also is not unusual. The last symptoms, are disorder of vision due to paralysis of accommodation, and aphonia due to the dryness and to paralysis of the muscles innervated by the inferior laryngeal.

Toxic Effects of Atropia.—Very important information as to the

action of atropia is obtained by a study of the toxic effects in animals and in man.

When atropia is administered by subcutaneous injection to warm-blooded animals, effects are produced very similar to those I have already described as occurring in man. I have made six experiments upon cats. The results of these experiments were so uniform that I need not occupy space to give each in detail. When one-fourth to one grain of sulphate of atropia is administered to a cat, the first effect which follows is a peculiar dryness and pallor of the mucous membrane of the lips and mouth. The lips move with difficulty, and have a dry and shrivelled appearance. The eyes become dry, and the palpebral opening is diminished in size. Dilatation of the pupil then occurs. As in frogs, defects of co-ordination first appear in the hind extremities, next partial paralysis extending finally to the upper extremities. When paralysis in all the extremities ensues, sensibility is not abolished. Even when complete anæsthesia of the cornea is produced, and no reflex movements of the eyelids can be excited, irritation of the roof of the mouth causes reflex movements of the jaws. The action of the heart is always considerably increased and the temperature elevated. A thermometer placed in the rectum exhibits an average rise in temperature of one-fourth of 1° F., whilst on the surface, the average increase of temperature is 1° F. Defects of vision, paralysis of accommodation, occur, as may be seen in the failure of the animal to avoid any obstacle, as a table leg. Hallucinations also occur, as evidenced by such movements as watching imaginary objects in the air, moving the head to avoid contact with them, and raising the fore-legs to strike. Injection of the conjunctivæ takes place, and the dryness of the eye yields to lachrymation. Urine and fæces are passed when poisonous effects are fully manifest. The urine instilled into the eye of another cat causes dilatation of the pupil.

The pupil contracts at the moment of death. The body is completely relaxed immediately after death, but extreme post-mortem rigidity sets in in a half-hour.

The morbid appearances after death are, congestion of the meninges and of the choroid plexus, congestion of the lungs, the large venous trunks gorged, and the left cavities of the heart empty.

The symptoms of poisoning, as observed in man, closely correspond to those which I have described as occurring in animals. To avoid tiresome details, I give, in the briefest manner, those symptoms of poisoning which I have happened myself to observe,

together with an analysis of such as have been reported by others. The following are the toxic effects of atropia as observed in man:—

Extreme dryness of the mouth; retraction of the lips; dysphagia and aphonia, consequences of the dryness of the mucous membrane, and paralysis of the pharyngeal and laryngeal branches of pneumogastric. Pupils largely dilated; conjunctivæ dry; eye prominent and brilliant; presbyopia; dimness of sight; spectral illusions; blindness. Hallucinations; pleasing delirium, sometimes maniacal excitement, sometimes stupor; vertigo; paralysis of sensory nerves; trembling; loss of cöordinating power; paralysis of motor nerves. Rapid pulse; rise in external temperature; flushing and burning of face. Frequent micturition; strangury; involuntary discharge of feces.

After death, extreme post-mortem rigidity; congestion of the meninges of the brain; congestion of the lungs; fulness of the great venous trunks; empty left cavities of the heart.

Conclusions.—Sufficient data have now been accumulated to enable me to state somewhat more definitely the nature of the phenomena produced by atropia.

By Lemattre, atropia is supposed to have a selective action upon the cerebral lobes, the pons, and especially upon the gray matter of the spinal cord. It has been shown that atropia has a special affinity for nervous matter. It cannot be doubted that atropia circulating in the blood affects, more or less, all parts of the nervous system. Indeed, the result of its action confirms this view. Delirium, loss of sensibility and motility, abolition of the special senses, show the influence of atropia upon the nervous system of animal life. The hallucinations, the fantastic images, the illusions are, in part also, due to deranged accommodation, to the presbyopia, and to the indistinctness of images in consequence of congestion of the retina.

The cerebral phenomena produced by it seem to me largely dependent upon the increased amount of blood which is pumped into the brain—congestion of the meninges being the principal lesion found after death. An altered state of the functions of the brain is the result of increased blood supply. Two factors are concerned in the causation of this congestion: increased arterial tension, and increased *vis-à-tergo*. It is obvious that mere congestion of the meninges and of the choroid plexus could not produce the phenomena characteristic of atropia poisoning. To this con-

dition must be added the direct impression of atropia upon the secreting cells of nervous matter.

Further, the facts show that whilst atropia acts as a depressor of the cerebro-spinal nervous system, it increases the functional activity of the organic nervous system. This latter influence is exhibited in the contraction of the radiating fibres of the iris; in the diminution in calibre of the arterioles; in the increased action of the heart; in the rise in bodily heat; in the irritability of intestines and bladder.

After a time, greater or less, according to the quantity administered, atropia exhausts the excitability of the organic nervous system, and a state of depression succeeds to the increased functional activity. If this were not so, it is difficult to conceive how atropia could produce a fatal result, except in enormous doses, for one class of actions is opposed to the other. A correct appreciation of these actions is of great importance in determining the nature of the physiological antagonism between atropia and other narcotics.

CHAPTER II.

ATROPIA AND PHYSOSTIGMIA.[1]

The opposite effects of atropia and physostigmia on the pupil are so striking, that a physiological antagonism extending throughout the whole range of their action, would seem to be probable. The dilatation of the pupil as produced by atropia is due, as shown in the preceding pages, to contraction of the radiating fibres of the iris. As the circular fibres of the iris are innervated by the third pair, the contraction of the pupil produced by physostigmia must be due, either to paralysis of the sympathetic or to excitation of the sphincter muscle. These two agents must, therefore, act oppositely upon the sympathetic system, or one must act upon the sympathetic and the other upon the nervous system of animal life.

Dr. Fraser,[2] of Edinburgh, has published an admirable paper

[1] The Physostigmia (calabarine) employed in these researches was made by Merck, of Darmstadt, who enjoys a deservedly high reputation on the continent of Europe for his pharmaceutical preparations.

[2] Abstract of Dr. Fraser's paper in American Journal of the Medical Sciences, April, 1868.

upon the physiological effects of the extract of Calabar bean. I shall avail myself of his very exhaustive labors, assuming that what he has informed us of the action of Calabar bean is entirely correct. I take this position the more readily, because my own observations with this agent are entirely in accord with Dr. Fraser's. In order to a more ready comprehension of the reactions which ensue when these two agents are conjointly administered, I place in parallel columns the principal physiological effects of each:—

ATROPIA.	PHYSOSTIGMIA.
A spinal paralyzer.	A spinal paralyzer.
Destroys excitability of motor nerves.	Destroys excitability of motor nerves.
Destroys the muscular irritability.	Preserves the muscular irritability.
Destroys the excitability of the sensory nerves.	Increases rather than diminishes the excitability of the sensory nerves.
Increases the action of the heart and the arterial tension, by an excitation of the sympathetic. Increases action of heart after division of pneumogastric.	A large dose produces cardiac syncope; action of heart ceases in diastole. This effect is not produced through the pneumogastric, although this nerve is ultimately paralyzed, for it follows when the pneumogastric is divided, nor does it result from paralysis of respiration. The cardiac syncope is due to a direct action on the cardiac ganglia.
	Diminishes arterial tension.
Increases respiratory movements.	Paralyzes muscles of respiration.
Dilates the pupil.	Contracts the pupil.

We have now the data for estimating the influence which these agents exert upon each other, when administered together.

Experiment.—Injected under skin of a frog 80 minims of a solution containing $\frac{1}{48}$ of a grain of physostigmia and $\frac{1}{24}$ of a grain of atropia. In fifteen minutes there was complete paralysis of the hind extremities and partial paralysis of arms. Sensation was not abolished, for when the skin was pricked, or muscles pinched, the frog attempted to escape. Soon after, however, on pinching an extremity the limbs were agitated by violent tetanic spasms, especially the upper. A slight tap on the back produced these effects: closure of eyelids, a sharp cry, opisthotonos, and tetanic rigidity of the limbs. Meanwhile the frog lay completely relaxed without the least motion. When taken by the head and raised up, the limbs hung down perfectly flaccid. A quick sudden blow, however, induced the tremors and the tetanic shocks. He lay in this condition a half hour apparently dead, when I inserted under the skin of the thigh $\frac{1}{4}$ of a grain of the sulphate of atropia. Re-

turning to the room after an absence of two hours, I found that all the toxic symptoms had disappeared; the frog jumped and was as active and lively in every respect as before the experiment commenced.

Experiment.—Injected as before under the skin of a frog $\frac{1}{16}$ of a grain of physostigmia. Paralyzing effects were manifest in three hours. Then injected $\frac{1}{12}$ of a grain of atropia (sulphate). Soon after the atropia was administered, the frog, when struck a quick, slight blow, uttered a cry, and was agitated by sudden tonic contractions of all the muscles. Slow and gradual pressure with the fingers did not produce these tetanic convulsions, but a quick tap on any part of the body gave rise to them. Then injected an additional $\frac{1}{12}$ grain of sulphate of atropia. A succession of tremors soon after agitated all of the muscles, especially those of the thigh, the limbs and body being all the time perfectly limp and flaccid. When the tremors ceased, no tetanic spasms could be induced by a blow upon any part of the body. The frog then became entirely insensible to irritants, and appeared to be without life. On opening the chest, however, the heart was found to be pulsating strongly and equably 52 per minute.

Experiment.—To a cat administered $\frac{1}{8}$ of a grain of sulphate of atropia by subcutaneous injection. The usual toxic effects manifested themselves in a few minutes: dryness of mouth; redness and injection of the fauces; dilatation of pupils; partial paralysis of hind extremities; sensibility to touch, to pain, and especially to temperature diminished; reflex movements normal. Injected then $\frac{1}{8}$ of a grain of calabarine. In five minutes decided contraction of the pupil occurred; paralysis of all the muscles of animal life took place so that the cat hung perfectly limp and flaccid when suspended by the ears; occasional tremors, especially of the limbs, and slight tetanic spasms on irritation of surface occurred, notwithstanding the complete paralysis; respirations grew slower and slower, and after the lapse of three hours occurred only at the rate of one in five minutes; action of heart continued, but gradually lost power and diminished in frequency of pulsations; complete anæsthesia of cornea; reflex and accommodative movements of the eye finally abolished. Respiration ceased before action of heart.

In subsequent experiments I varied the proportions of atropia and calabarine (physostigmia) in order to ascertain how far these agents were antagonistic as to toxic power. Thus to a large and powerful cat I administered by hypodermic injection $\frac{1}{2}$ of a grain

of sulphate of atropia, and $\frac{1}{24}$ of a grain of physostigmia. The symptoms of atropia poisoning were first manifested, and afterward the effects characteristic of physostigmia, without, however, producing a fatal result. In corresponding doses physostigmia is more powerful than atropia; hence in order to obtain a balance of physiological effects, sufficient atropia must be administered to produce some dilatation of the pupil, and as physostigmia is slower and also longer in action, the effect of the atropia must be maintained by continued use. If a quantity of physostigmia, just sufficient to produce a fatal result, be administered, its toxic power may be counterbalanced by atropia given so as to maintain a slight degree of dilatation of the pupil. Large quantities of both these agents, administered simultaneously, so overpower the nervous centres (the cerebrum and respiratory centre) as to destroy life.

The results then of the study of the mutual reactions which obtain between atropia and physostigmia when administered together, may be stated as follows:—

Atropia and physostigmia are not antagonistic as regards their action upon the muscular system of animal life—paralysis being induced by both. Atropia produces paralysis by destroying the muscular irritability and the excitability of the motor nerves; physostigmia by paralyzing the spinal cord.

Atropia and physostigmia are antagonistic as regards their action on the sensory nerves; atropia destroying and physostigmia heightening the sensibility of these nerves.

They are antagonistic as to their influence over the respiratory movements; atropia increasing and physostigmia retarding them.

They are antagonistic in their action upon the heart; atropia producing excitation of the cardiac ganglia, and physostigmia paralyzing these ganglia.

They are opposed in respect to their action on the sympathetic; atropia producing increased action of the sympathetic; physostigmia paralyzing this system.

They have opposite effects on the pupil in virtue of opposite effects on the sympathetic; atropia dilating the pupil by its action on the radiating fibres of the iris; physostigmia contracting the pupil by paralyzing the radiating fibres.

A very singular effect, which I was not prepared to find, is the peculiar exaltation of the reflex faculty produced in frogs, when these agents are administered together—a sudden irritation of the surface causing tetanic rigidity like electric shocks, the muscles

immediately afterward resuming their very relaxed and flaccid condition. Atropia sensibly weakens, although it does not abolish entirely, the reflex faculty; physostigmia destroys the reflex faculty; yet the combination of the two agents produces effects not unlike those of strychnia. The analogy is preserved even after death, for post-mortem rigidity sets in at once and is very decided. The tetanic spasms must not be confounded with the tremors which are characteristic of physostigmia. These tetanic spasms are less marked in warm-blooded animals, but they nevertheless occur to a limited extent, and after death a marked degree of rigidity exists, the head and neck being curved back and the feet turned in.

CHAPTER III.

ATROPIA AND STRYCHNIA.

As atropia produces paralysis and strychnia tetanic rigidity of the muscles, these agents may be supposed to possess properties physiologically antagonistic. The distinctive effect of strychnia is to increase the reflex excitability of the spinal cord. Schroeder Van der Kolk[1] has shown that it has a selective action upon the medulla oblongata, causing dilatation of the minute vessels. This is in accordance with the opinion of Brown-Séquard, who considers the peculiar properties of strychnia due to increased nutritive activity of the cells of the cord resulting in an exaltation of the reflex faculty. Strychnia does not destroy the excitability of nerves, or the irritability of muscle. In all of these respects the actions of strychnia are opposite to those of atropia, except in respect to the reflex faculty—for as my experiments on warm-blooded animals prove, atropia does not abolish the reflex faculty of the spinal cord.

I have undertaken a series of experiments to determine the nature of the reactions which ensue when atropia and strychnia are conjointly administered. I employed cats for these experiments. The results were so uniform that I need not waste space in a recital of the details of the experiments.

[1] On the Minute Structure and Functions of the Medulla Oblongata, Syd. Soc. Ed.

Experiment.—Injected under skin of a kitten $\frac{1}{12}$ of a grain of atropia (sulphate) and $\frac{1}{20}$ of a grain of strychnia (nitrate). The usual symptoms of atropia poisoning followed in five minutes; dilatation of the pupil; retraction of lips and dryness; dryness of mouth and conjunctivæ; injection of fauces; disorders of movement (loss of co-ordination); partial paralysis of extremities. At the end of ten minutes, muscular twitchings began at the seat of puncture and radiated from that spot over the body. The spasms were clonic in character and irregular. When the cat was not disturbed, her chief distress seemed to be from the atropia, but when required to move, she ran violently across the room, her extremities and tail agitated by strong convulsive tremors. A strong convulsion produced death by spasm of muscles of respiration in about fifteen minutes after the injection. The body remained quite flaccid for a half-hour after death, when decided post-mortem rigidity occurred. Pupils remained dilated.

The same facts were developed by several experiments. We learn from these that atropia and strychnia are not antagonistic as to toxic power, for although some of the phenomena of strychnia poisoning were modified, yet the fatal result was not prevented—not even postponed. Atropia acted more speedily. The strychnia injection did not affect the symptoms produced by atropia. The local action of the strychnia, the spasms commencing at the site of the injection, is an interesting fact. The spasms themselves, were modified by reason of the paralyzing action of atropia on the motor nerves and the muscular irritability.

Dr. Spence,[1] of Edinburgh, who has lately investigated the physiological effects of strychnia, thinks that erroneous notions have existed in regard to the quantity of strychnia necessary to produce death in the cold-blooded animals, and hence the conclusions which have been formed as to the antidotal power of woorara and nicotine, are fallacious. Dr. Frazer has shown that Calabar bean is the physiological antagonist of strychnia. Theoretically considered, a combination of atropia and physostigmia would seem to fulfil the indications more perfectly, but practically we find that atropia and physostigmia produce tetanic rigidity strongly resembling that caused by strychnia.

In a case of paralysis—hemiplegia—accompanied by *late rigidity,* as Dr. Todd[2] has styled it, I have injected simultaneously $\frac{1}{48}$

[1] Medical Times and Gazette, June 16, 1866.

[2] On the Nervous System. Am. Ed.

of a grain of atropia and the same quantity of the nitrate of strychnia. The two agents under these circumstances produced their characteristic effects, apparently uninfluenced by each other. The rigidity, as well as the hyperæsthesia which accompanied it, were relieved by the atropia. These states of the paralyzed parts had not been affected by previous injection of the strychnia alone.

CHAPTER IV.

ATROPIA AND PRUSSIC ACID.

It has recently been asserted by M. Preyer[1] that atropia is the physiological antidote to prussic acid. He was conducted to this conclusion by reflecting upon the mode in which prussic acid produces death. As prussic acid in large doses causes paralysis of the heart, he assumed that an agent which would paralyze the pneumogastric, the inhibitor nerve of the heart, and at the same time "stimulate the central nervous apparatus of respiration" would prove to be the true physiological antidote. He, however, prudently restricts the use of atropia to those rare cases of poisoning by prussic acid, in which "there is apnœa and the heart remains beating."

There are various theoretical considerations opposed to this view. Piotronosky[2] affirms that he has produced tetanic spasms of the heart and wrinkling in the transverse folds of its external fibres, by direct irritation of the vagus. This experiment is submitted in proof of the statement that the external fibres of the heart are innervated by the vagus and the internal by the sympathetic. If this be the case, it is obvious that an agent which simply paralyzes the terminal filaments of the pneumogastric, would not supply the effect required. Moreover, division of the pneumogastric produces decided slowness of respiration, after having for a short period quickened it somewhat. Further, atropia has little influence over the respiratory movements. Its real power consists in excitation of the cardiac ganglia of the sympathetic, and whatever of physiological antagonism there is between atropia and prussic

[1] The Practitioner, Aug. 1868.

[2] Sydenham Society Biennial Retrospect, 1867, p. 123.

acid must be referred to the difference in their action upon the heart.

Theoretical considerations must yield to the demonstrations of experiment. Mr. Preyer has demonstrated on rabbits and guinea pigs, that the subcutaneous injection of small quantities of atropia is an unfailing antidote to prussic acid if employed quickly after the injection of the acid. I have submitted this statement to the test of experiment.

Experiment.—I passed into the throat of a pigeon, by means of a pipette, 5 minims of medicinal prussic acid (U. S. P.) and immediately injected $\frac{1}{24}$ of a grain of sulphate of atropia. The bird had in a few minutes convulsive movements of the head, neck and eyelids; fell down, and expired in a general convulsion of a tonic character.

The fatal result in the preceding experiment may be attributed to the atropia. In order to obviate this objection, I changed the order of administration of these agents. As pigeons are not very susceptible to the action of atropia, I also increased the quantity administered by subcutaneous injection.

Experiment.—Administered to a pigeon by subcutaneous injection one-eighth of a grain of atropia. When the influence of this began to be manifest, passed into the gullet by a pipette, 5 minims of the medicinal hydrocyanic acid. Death ensued precisely as in the first case.

It may be urged against these experiments that pigeons are not suitable subjects. As cats are readily affected by both these agents, in my subsequent experiments I employed these animals. The details of the experiments and the results being so uniform, I need narrate but one as a type of all.

Experiment.—Administered by subcutaneous injection to a cat one-fourth of a grain of atropia. When the symptoms characteristic of atropia poisoning were produced, I poured into the gullet 10 minims of medicinal hydrocyanic acid. The cat fell upon her side, had a few convulsive twitches of the extremities, uttered a sharp cry and expired.

In these experiments on cats, I preferred to bring them under the influence of atropia before administering the prussic acid, because of the great difference in the rapidity with which these agents act. If there really existed a true physiological antagonism between them, there could be no difference in result whether atropia or prussic acid were first administered. It is clear, I think,

that no such antagonism exists as supposed by M. Preyer, but it may be admitted that atropia will be useful in counteracting the depression of the heart's action in those rather exceptional cases in which the symptoms of poisoning are delayed, or in those cases in which just sufficient prussic acid has been administered to produce dangerous symptoms, there being time enough to employ cardiac stimulants.

CHAPTER V.

ATROPIA AND MORPHIA.

THE physiological antagonisms examined in the preceding chapters, are by no means equal in interest and practical importance to those now to be examined, between atropia and morphia. Although the subject of the antagonism of atropia and morphia has been studied with extraordinary diligence and success, it cannot be said that all questions in respect to it have been definitely settled. I, therefore, venture to offer some additional observations on this important topic.

There are yet those who deny that any real antagonism exists between morphia and atropia. Thus, Dr. John Harley,[1] one of the most recent investigators, concludes that "as far as a hypnotic influence is concerned, belladonna decidedly increases the effects of opium, and, on the other hand, opium invariably intensifies not one or two, but *all* the effects of belladonna."

Also Dr. Brown-Séquard,[2] who says that "death by opium takes place from the same dose whether we simply employ belladonna or not. These experiments clearly establish that the toxic effects of these poisons, in certain animals at least, do not neutralize each other." The same conclusion is arrived at by Onsum.[3] Dr. Bois,[4] who has lately examined this question experimentally by the successive injection of large doses of atropia and morphia, affirms that

[1] Gulstonian Lectures, Medical Times and Gazette, April 4, 1868.

[2] Lectures on the Diagnosis and Treatment of Functional Nervous Affections. Phila., 1868. Part I. p. 78, foot-note.

[3] Schmidt, Jahrbücher, vol. 128, p. 288.

[4] Gazette des Hôpitaux. Quoted by Lemattre, Arch. Gén. Anat., 1865.

the toxic effects of these agents are increased by simultaneous use. Such is the conclusion, indeed, of all experimenters who have studied the effects of atropia and morphia in animals. Notwithstanding the unanimity on this point, I have made a series of experiments to satisfy myself. I need not waste space by narrating these experiments in detail.

Experiment.—When full doses of atropia and morphia—one-eighth of a grain of the former, and one grain of the latter—are administered by subcutaneous injection to a kitten, the effects of the atropia are first manifested. In five minutes pupils dilate, lips grow dry and retract, and fauces become red. Loss of power in hind extremities occurs soon after. The animal utters loud cries in a somewhat husky voice at intervals. Respiration grows hurried and action of the heart increases. The animal manifests great uneasiness and alarm, and runs to and fro without object, striking against chair and table-legs. The limbs in running are agitated by irregular convulsive movements. Reflex movements of the eyes become slow and feeble, and finally are abolished. Rhythmical movements of the jaws, and rapid striking of the teeth, with frothing at the mouth, are observed. The especial sensibility of the auditory nerve is heightened, so that the least noise alarms the animal, and she rushes to and fro to escape the imaginary danger, the movements of the limbs being disorderly and little under control. Sensibility is much diminished. Death occurs in about two hours in a convulsion, after a more or less prolonged period of deep somnolence.

Atropia and morphia uniformly produce a fatal result, when administered in toxic doses to cats. I find, however, that if a dose of morphia just sufficient to destroy life be administered, a fatal result may be prevented by the use of atropia. This result, so opposed to the observations of other experiments, needs explanation. My method of proceeding in order to determine this, was to administer one grain of sulphate of morphia, and then to await the development of the toxic effects before injecting the solution of atropia. I then injected a small quantity of atropia—$\frac{1}{48}$ of a grain—sufficient to cause a slight degree of dilatation of the pupil. This amount was injected from time to time—two or three times—so as to maintain the full effect of the atropia without at any period suddenly charging the nervous centres with an amount of the toxic material too great for them to bear. Proceeding in this way carefully, I found that the toxic effect of morphia may be overcome,

the animal suffering at last only from the physiological effects of atropia—dryness of mouth, dilatation of pupil, injection of conjunctivæ, and some disorders of sensation and voluntary movement. If great care be not exercised in the use of the atropia, the life of the animal will finally be destroyed by this agent, for the effects of this last much longer than those of morphia. Sufficient atropia only is necessary to maintain the action of the heart and the peripheral circulation, and not in such quantity as to overwhelm the brain. The state of the pupil is the guide, but the too common error of giving sufficient atropia to cause extreme dilatation of the pupil, should not be committed: the contraction of the pupil caused by morphia should only be overcome. In other words, the toxic effects of atropia should not be superadded to the morphia poisoning.

Atropia acts against morphia poisoning, by promoting elimination. This action was long ago pointed out by Bernard, in his study of the antagonism between curara and strychnia. "Curara," says Bernard, "promotes the elimination of strychnia, by the increased activity which it gives to all the secretions, especially the urinary secretion." In my experiments on cats I have sought to give the atropia at a period, in the course of the toxic symptoms produced by morphia, most favorable for elimination. The arrest of the urinary secretion produced by morphia, and the increased activity of the kidneys caused by atropia, are capital points in respect to the physiological antagonism of opium and belladonna.

The reciprocal influence which atropia and morphia exert upon each other has been elaborately studied by trials upon man. When $\frac{1}{4}$ of a grain of morphia and $\frac{1}{96}$ of a grain of atropia are injected under the skin, the following are the phenomena observed: a sense of depression at the epigastrium; gurgling of the intestines (borborygmi); slight nausea; a feeling of distension of the brain, with a rushing noise in the ears and vertigo; dryness of the lips, and afterwards of the mouth and fauces; voice husky; swallowing difficult; no change of the diameter of the pupil; pulse increased somewhat in frequency and in volume; respirations deeper and a little slower; the fulness of the head and the vertigo, increased so that locomotion becomes uncertain and staggering; itching of the whole cutaneous surface; bladder irritable and emission of urine slow and difficult; more or less somnolence, and in some persons sleeplessness, but a feeling of great comfort and freedom from suffering; perspiration; nausea and vomiting; dizziness; mental hebetude; muscular soreness and weakness.

The foregoing phenomena are mentioned in the usual order of their occurrence. The effects of the injection last from twelve to eighteen hours, according to the susceptibility of the individual. In many persons, the first impression of the atropia and morphia is marked by nausea and vomiting, but this is much more frequently the case with morphia alone. As the influence of the injection declines, some persons experience great nausea, often vomiting, vertigo, and general *malaise*. But these unpleasant effects are rather due to idiosyncrasy, and are observed in but a small proportion of those operated upon.

The period within which, after the injection is administered, the peculiar effects begin to be manifest, varies a little in different individuals according to their susceptibility. In those accustomed to the influence the impression does not occur so early, and comes on in an equable and orderly manner; on the other hand, those unaccustomed to it feel the action quickly—in a few seconds—and the maximum effect is attained in fifteen minutes. The effect of the morphia declines first. Dryness of the mouth, aphonia, and a slight degree of dilatation of the pupil remain after the effects of the morphia have ceased. The hypnotic effect is a prominent result. This is a more constant result of the use of atropia and morphia than of morphia alone.

A very important question is the influence of morphia and atropia when conjointly administered, upon the action of the heart and the arterial tension. Atropia, as has been distinctly shown in a previous part of this paper, greatly increases the action of the heart and the arterial tension. According to Mitchell, Morehouse, and Keen,[1] morphia does not counteract the stimulant action of atropia on the pulse. Erlenmeyer,[2] on the other hand, states that although they do not wholly counterbalance each other's effects on the pulse, yet the stimulant action of the atropine when given alone is so modified that an effect intermediate between the depression caused by morphia and the excitement caused by atropia, is the result. Harley[3] asserts that atropia overcomes the depression of the heart's action caused by morphia. He attributes this result to the fact that the powerful stimulation of the sympathetic exerted by atropia, overcomes the derangement of the vagus nerve pro-

[1] American Journal of the Medical Sciences, July, 1865.

[2] Die subcutanen Injectionen der Arzneimittel, von Sanitätsrath Dr. Erlenmeyer, Leipzig, 1866, p. 58.

[3] Medical Times and Gazette, op. cit., April 4, 1868.

duced morphia. My own observations are opposed to those of Mitchell, Morehouse, and Keen, and confirmatory of those of Erlenmeyer and Harley. In order to place these conclusions before the reader in a more satisfactory manner, I subjoin some sphygmographic tracings. For the purpose of comparison I give some tracings showing the action of atropia when administered alone.

No. 1.

No. 1. Before atropia; pulse 75.

No. 2.

No. 2. In forty-five minutes after atropia; pulse 112.

No. 3.

No. 3. Before atropia—another patient.

No. 4.

No. 4. In five minutes after atropia.

The next tracings were taken from a patient to whom had been administered, by subcutaneous injection every night for two months, $\frac{1}{2}$ grain of sulphate of morphia and $\frac{1}{24}$ of a grain of sulphate of atropia.

No. 1.

No. 1. Before atropia and morphia; pulse 76.

No. 2.

No. 2. In twenty minutes after atropia and morphia; pulse 96.

No. 3.

No. 3. In twenty-five minutes after atropia and morphia; pulse 96.

The difference between the action of atropia alone and atropia and morphia, as exhibited by the sphygmograph, may be stated as follows:—

Atropia.	Atropia and Morphia.
First increases length of pulse-wave and afterwards decidedly diminishes it.	Length of wave slightly diminished.
The ascent of the wave is less abrupt, the summit more rounded, and the descent more gradual.	Little effect upon character of wave.
The dicrotism diminished in intensity.	Dicrotism not at all or but slightly affected.

These results may be formulated as follows: atropia increases the cardiac movements and raises the arterial tension; morphia moderates the increased action of the heart, and counterbalances, although not wholly, the increased arterial tension produced by atropia.

As many of the secondary effects of atropia are due to the increased rapidity of the circulation and increased arterial tension produced by it, morphia within certain limits will exert a modifying influence upon these effects. The delirium produced by atropia is largely dependent upon the altered state of the intra-cranial circulation. Morphia by decreasing the number and force of the cardiac pulsations and by lowering the arterial tension, lessens so much of the cerebral effects of atropia as may be due to the changes in the intra-cranial circulation produced by the latter. These physiological conditions find expression in the greater hypnotic, but less toxic power of morphia and atropia, than of atropia alone. In my observations on animals and on man more or less deep somnolence was produced by the conjoined use of atropia and morphia. Brown-Séquard[1] affirms that these agents are antagonistic as regards their effects upon the brain, and that "in consequence of this antagonism the dose of opium to procure sleep ought to be greater than usual if belladonna is employed with it." According to Drs. Mitchell, Morehouse, and Keen,[2] "the cerebral symptoms caused by either

[1] Diagnosis and Treatment of Functional Nervous Affections, op. cit. p. 79.

[2] Am. Journal of the Medical Sciences, op. cit.

drug are, to a great extent, capable of being overcome by the other." The same opinion has been expressed by Erlenmeyer.[1] Those who have seen cases of opium or belladonna poisoning in which the physiological antidote was employed, have been conducted to the same conclusion. I have already quoted the statements of Harley,[2] that "opium intensifies not only one, but *all* of the effects of belladonna." In another place he states a fact which I am able to confirm, that patients who cannot be made to sleep by opium, are made to sleep by opium and belladonna combined. An instructive case has happened under my observation, which seems to me to illustrate some of these disputed questions.

A feeble patient, suffering under phthisis, had a harassing cough for which I administered hypodermic injections of morphia. The effect not being sufficient, I increased the dose, and as the event proved, incautiously. At 9 P. M. I gave him 30 minims of a solution of 16 grains to the ounce=1 grain. In ten minutes he fell asleep sitting up in bed and in the act of talking to his wife. She, surprised at the sudden effect, but not alarmed, laid him down. At the end of two hours, observing that he breathed slowly and was very pallid, she attempted to arouse him, but found that he was entirely unconscious. I saw him at 12 M. when he was in the following condition: breathing slowly and irregularly—10 per minute; pulse 60 and very feeble; could not be roused; pupils contracted and eyes turned up; no reflex movements of eyelids could be induced by any irritation; skin cool and perspiring. I waited a half-hour and then tried to arouse him by shouting in his ear and by irritation of his skin; no effect was produced, but the coma was evidently deepening and his vital powers failing. I could not put in force the usual measures for relief of opium narcosis, owing to his extreme debility. Without attempting any other expedient, I injected $\frac{1}{24}$ of a grain of sulphate of atropia and awaited with some anxiety its action. In fifteen minutes his pulse rose to 80: his skin grew warm and dry; his face flushed a little; pupils dilated, and the conjunctivæ became somewhat injected. In a half-hour he began to cough, and manifested a sense of suffering by corrugation of the eyebrows; his respirations had then risen to 14, and were more regular. In two hours reflex movements of the eyelids could be exhibited by touching them; but he could not

[1] Die subcutanen Injectionen der Arzneimittel, op. cit.

[2] Medical Times and Gazette, April 4, 1868, p. 377.

yet be roused. He continued to sleep until 4 P. M., when he was easily awakened, but he remained in a more or less somnolent condition for twelve hours longer. The whole duration of the period of narcosis was twenty hours, during which he was entirely unconscious, and insensible to irritants. His conjunctivæ were injected, his mouth dry and his voice husky, and his vision disordered at the end of forty-eight hours. During the period of narcosis, no evacuation took place, but at the end of twenty hours he passed a large quantity of urine, but slowly and with difficulty.

The facts in the foregoing case are all the more satisfactory, because no other means of treatment were, or, indeed, could be adopted. There can, therefore, be no question as to the influence of atropia in counteracting many of the effects produced by the morphia. The action of the morphia appeared to be modified by the atropia in respect to—

1. The state of the pupil.
2. The action of the heart.
3. The arterial tension.
4. The respiratory movements.
5. The temperature, or body heat.
6. The circulation and functions of the skin.
7. The reflex faculty.

The action of the morphia was either not affected or increased by the atropia in respect to—

1. The hypnosis.
2. The dryness of the mouth.
3. The dysphagia and aphonia.
4. The dysury.

The effects of $\frac{1}{24}$ of a grain of atropia lasted twelve hours longer than those produced by one grain of morphia. The last effect to disappear was the disorder of accommodation. My patient complained of dimness and uncertainty of vision, and was presbyopic when all the other phenomena had disappeared. The dimness of vision appeared to be in part due to congestion of the fundus of the eye, for this symptom persisted so long as the injection of the conjunctivæ continued. In a patient, already referred to, to whom I gave hypodermic injections of atropia and morphia for several months, the presbyopic state continued notwithstanding these agents counterbalanced each other, as respects the state of the pupil, showing that although morphia produces spasm of the

muscle of accommodation, as stated by Græfe, yet atropia overcomes this.

Conclusions.—Atropia and morphia, when administered simultaneously, or one during the action of the other, exert a distinctly modifying influence upon each other.

They are antagonistic as regards their action on the pupil, but morphia does not overcome the presbyopia caused by atropia.

They are to a certain extent antagonistic in their action on the heart; morphia diminishing the stimulant effect of atropia, producing an effect intermediate between the slow pulse of the one and the quick pulse of the other.

Morphia slows the respiration and atropia quickens it; when administered together, the result is an action intermediate.

Morphia does not counterbalance the redness of the skin, its increased temperature, and the general rise in body heat produced by atropia. The sweating caused by morphia is prevented by atropia. Morphia diminishes but does not prevent the increased arterial tension caused by atropia.

When administered by subcutaneous injection, atropia diminishes the sickness, and prevents the depression of the heart's action, caused by morphia.

Atropia intensifies the purely hypnotic effect, but diminishes the coma and relieves the insensibility produced by morphia.

They are not antagonistic, but allies in their effects upon pain.

Morphia does, and atropia does not, destroy the reflex faculty.

The dryness of the mouth, the dysphagia and aphonia of atropia are not diminished but increased by morphia.

They are antagonistic in their action on the intestinal canal; morphia constipating and atropia relaxing the bowels.

The dysury caused by atropia is not relieved by morphia.

They are antagonistic as regards their action on the kidneys; atropia increasing and morphia diminishing the flow of urine.

They differ in the period of access, and in the duration of the symptoms respectively caused by them; atropia acts more speedily, and its action continues longer.

So far as these agents are capable of counterbalancing each other, the effect of $_2{}^1{}_4$ of a grain of atropia is equal to one grain of morphia.

PART II.

THERAPEUTICS OF ATROPIA.

CHAPTER I.

ATROPIA ALONE AND IN COMBINATION.

From the point of view of rational therapeutics, the study of the actions of atropia is very satisfactory; for upon existing knowledge of its physiological effects are based its best established therapeutical uses. It is no part of my purpose to discuss those uses of atropia—the offspring of a blind empiricism—which have no support in any of its physiological actions. I therefore pass over those so-called *alterative* effects which have been attributed to it, because they are too little supported by authentic clinical facts. I also pass over those uses of atropia so important to the ophthalmologist, not only in respect to the operations upon, but in the diseases of the eye. This branch of the subject I confess my incompetence to treat in a satisfactory manner.

As a Remedy for Cardiac Neuroses.—Dr. Harley,[1] considers atropia a valuable cardiac stimulant. It is especially adapted to cases in which beside a feeble action of the heart, the capillary circulation is slow and imperfect. Its use is contraindicated in narrowing and obstruction of the aortic orifice, and in cases of mitral disease with dilated right cavities, as I have ascertained by personal observation, for, under these circumstances, greater rapidity of the circulation only increases the existing cardiac lesions and adds to the distresses of the patient. It is a suitable cardiac stimulant in those conditions of depression, the causes of which are not resident in the heart itself, such as poisoning by organic alkaloids, in which the chief danger consists in a paralysis of the heart. So also the depression consequent upon severe injury, or surgical operations, may be relieved by the use of atropia. Since Dr. Greene of this country proposed the use, subcutaneously, of morphia to prevent

[1] Medical Times and Gazette, op. cit.

the sickness and depression which follow the inhalation of chloroform, I have employed atropia with a little morphia for the same purpose. This was a very valuable suggestion, but it is capable of wider usefulness than Dr. Greene indicated. The subcutaneous use of atropia before the administration of chloroform, lessens the dangers of paralysis of the heart, and of respiration. In order, therefore, not only to prevent the after ill-effects of chloroform inhalation, but to obviate the dangers of the inhalation itself, administer by subcutaneous injection $\frac{1}{60}$ of a grain of atropia, and $\frac{1}{8}$ to $\frac{1}{4}$ of a grain of morphia, ten or fifteen minutes before commencing inhalation. If, however, it may be considered desirable only to prevent the after-effects of chloroform inhalation, administer the above-named quantities before the effects of the anæsthetic have passed off. In most cases the anodyne effects of the hypodermic injection are equally desirable. Not only is there no antagonism between the chloroform anæsthesia and the pain-relieving and heart-sustaining influence of the atropia and morphia, but they mutually aid each other. The patients observed by me under these circumstances were immensely relieved, not only from the after-effects of the chloroform inhalation, but also from the pain and depression of the vital forces, usually following a surgical operation.

Atropia is a remedy of the greatest value in the treatment of *angina pectoris*, and the "restraint neuroses" of the heart. Many of these cases are free from any organic lesion of the heart discoverable by our present means of investigation, being dependent apparently upon an irritation seated in the semilunar ganglion, the solar plexus, or in the terminal filaments of the pneumogastric, and in a few instances probably due to lesion of a remote part of the sensory nervous system. The best method of administering atropia in these affections during the access of pain and uneasiness, is by hypodermic injection—the best method, both in respect to promptness and efficiency. When pain is a prominent feature, morphia may be combined with atropia advantageously. Treatment in the interval between the seizures is scarcely less important. As stated by Wilson Fox,[1] Handfield Jones,[2] Romberg,[3] Laennec,[4] and others, more or less serious functional disorder of the heart is

[1] System of Medicine, Reynolds, vol. ii. p. 823 et seq.
[2] Functional Nervous Disorders, Am. ed. p. 215.
[3] Nervous Diseases of Man, Sydenham Society Translation.
[4] Quoted by Romberg.

a very frequent symptom of stomach disease. Indeed, Handfield Jones expresses the belief that most cases of angina pectoris are of gastric origin. The cases produced in this way exist in varying degrees of severity, from simple irregularity in the heart's action to the severest spasm in which death seems imminent. Atropia, according to my observation, is the best remedy for these cardiac troubles. The alkaloid may be administered in combination with a mineral acid.[1] Trousseau[2] expresses great confidence in the internal administration of belladonna; but his opinion as to the hypodermic use of atropia is still more favorable. "The subcutaneous injection of atropia," says Trousseau, "inserted near the point of origin of the pains, and in the cervical and axillary regions, retards the return of the attacks, diminishes their violence, and finally cures them, if the neuralgia be not dependent upon an organic affection of the heart or great vessels." My own experience in these cases is entirely in accordance with this statement.

Atropia in the Respiratory Neuroses.—Belladonna has, for a long period, been employed in these affections. The greater activity and certainty of atropia, as well as its therapeutical power, render it more useful than the crude drug, or any of its pharmaceutical preparations. The hypodermic use of atropia alone, or combined with morphia in the treatment of the respiratory neuroses, especially asthma, is a very important addition to former methods. According to Erlenmeyer,[3] Oppolzer was the first to use atropia by subcutaneous injection for the relief of asthma. Prof. Courty,[4] in 1859, in the case of a lady aged 54, injected a solution of atropia over the pneumogastric nerve to arrest an asthmatic paroxysm. This practice does not appear to have been generally adopted—for our systematic works are silent on the subject. In the last American edition of Salter on Asthma no allusion is made to the hypodermic treatment of this disease. Having had considerable experience in the treatment of asthma by this method, I can speak with great confidence of its utility. A paroxysm of asthma may be quickly

[1] ℞.—Atropiæ, gr. j;
Acid. phosphor. dil. fʒss;
Aquæ, fʒvijss.—M.
S.—A teaspoonful twice daily in water.

[2] Clinique Médicale de l'Hôtel-Dieu de Paris, tome ii. p. 134 et seq.

[3] Die subcutanen Injectionen der Arzneimittel, op. cit. p. 66.

[4] Lancet, 129—1—1860.

ended by the subcutaneous injection of morphia and atropia.[1] In a few seconds after the injection, intestinal movements are excited, more or less loud gurgling occurs, abundant eructations of gas take place, and the patient experiences relief from the difficult breathing. A remarkable change is observed in the pulse; from being rapid and feeble, it becomes slower and fuller. The respirations are no longer laborious, and the diaphragm ceases its tumultuous movements. In from fifteen to thirty minutes after the administration of the injection, the patient is sufficiently relieved to lie down and sleep. But this treatment would be the less desirable, if it accomplished no more than the relief of the paroxysm. My own observation entitles me to say that it decidedly lengthens the interval between the seizures, and diminishes the violence of succeeding paroxysms. I am not prepared to say that spasmodic asthma may be cured in this way, no case having been under my observation a sufficient length of time, but the amelioration is so decided and so lasting as to justify confident expectations of procuring ultimate exemption.

In treating spasmodic asthma by the hypodermic method, it is better to anticipate the paroxysm. When the patient experiences the usual premonitions of an attack, a small injection will prevent its development.

The paroxysms of difficult breathing which accompany emphysema and mitral disease may also be promptly relieved by the subcutaneous injection of atropia and morphia, but in these cases the relief is more temporary. I have already indicated the reasons for caution in administering these injections in cases of mitral disease, and obstruction of the aortic orifice. They are not contra-indicated in cases of weakened walls and dilated cavities of the heart; although morphia alone is highly objectionable in these states.

Belladonna has long been employed in the treatment of hooping-cough. It is the best remedy for this disease, according to Trousseau,[2] and is strongly recommended by Brown-Séquard, who thinks to maintain the full physiological effects of this drug for a few days, is to bring about a cure. The alkaloid atropia is preferable to the crude drug, for the reason that it is more certain in its effects, and that a full physiological influence is more easily maintained by it.

[1] Atropia, $\frac{1}{48}$ to $\frac{1}{24}$ of a grain, morphia, $\frac{1}{8}$ to $\frac{1}{4}$ of a grain.

[2] Clinique Médicale, tome ii. p. 428.

A solution of the sulphate[1] may be used twice a day, or a combined solution of atropia and morphia. Or, this disease may be quickly cured by the hypodermic injection, as practised for asthma, the influence being maintained for several days. In children, however, a simple solution, used internally, is better, for the reason that it will be taken readily, and its effect may be easily graduated to the physiological capabilities of the patient. In treating hooping-cough it should not be forgotten that children are not very susceptible to the action of atropia, and hence the dose should be increased until decided effects are produced. It is necessary further to remember that the effects of atropia are so lasting that two doses daily are quite sufficient to maintain a full effect.

Spasmodic cough, *laryngismus stridulus*, and aphonia, dependent upon irritation reflected through recurrent laryngeal nerves, are much benefited by atropia, as I have found by personal observation.

Atropia in Diseases of the Respiratory Organs involving Structural Alterations.—The various forms of cough accompanied by free expectoration are much benefited by atropia. A dry state of the bronchial mucous membrane and irritative cough dependent thereon, are unsuitable for the action of atropia. I have observed remarkably beneficial results from the combined use of morphia and atropia[2] in cases of phthisis, accompanied by violent cough, profuse expectoration, and hectic. The cough and expectoration, the hectic and the exhausting sweats especially, are much relieved by it.

Trousseau[3] has used injections of atropia for the relief of pleuritic pain. Cases of pleurisy may be conducted to an early conclusion by subcutaneous injection of morphia and atropia in the doses recommended for asthma, but this treatment is not adapted to those cases in which effusion has occurred. The injection administered when the symptoms first make their appearance will often prevent any further development of the disease.

[1] ℞.—Atropiæ sulphat. gr. j ;
Aquæ destil. f℥j.—M.
S.—2 increased to 5 drops at a dose.

℞.—Atropiæ, gr. j ;
Acid. muriat. dil. f℥ss ;
Aquæ, f℥vijss.—M.
S.—2 increased to 5 drops at a dose.

[2] ℞.—Morphiæ sulph. gr. xvj ;
Atropiæ sulph. gr. j ;
Acid. acetic. dil. f℥j ;
Aquæ, f℥vij.—M.
S.—15 drops at a dose.

[3] Lancet, 129-1-1860.

Neuroses of the Digestive Organs.—I have used atropia with success in the treatment of gastralgia, and enteralgia. Cases of dyspepsia, in which pain is a prominent feature, are often much benefited by a combination of atropia and a mineral acid. Painful conditions of the semilunar ganglion and solar plexus, causing symptoms of angina pectoris are cured by atropia. In one very alarming case of this character, occurring in a physician, I used with complete success a combination of atropia and morphia administered hypodermically. In the obstinate constipation caused by lead, and in some cases of intussusception, this method of treatment has been indicated, but I am unable to speak from personal observation of its real utility.

Dr. Fuller,[1] observed sickness and diarrhœa in five of twelve children to whom he administered belladonna. Trousseau considers belladonna a most important remedy against constipation. Its *modus operandi* is quite plain: it increases the peristaltic movements by inducing contraction of the unstriped muscular fibre of the intestinal canal. For this, as indeed for almost all the purposes to which belladonna is applied, atropia may be substituted with advantage. In constipation dependent upon atony of the muscular layer of the bowel it is indicated, but it is not a purgative in the technical sense of that term. It may be combined with other purgatives to meet particular indications.[2] Atropia is especially valuable in the constipation of females suffering from uterine disorder of a painful character. Feeble digestion, constipation, languid circulation in the skin, scanty and painful menstruations—conditions frequently associated, are much benefited by the conjoined use of atropia and iron, or atropia and a mineral acid.

There is no remedy, in my experience, comparable to atropia in the treatment of the vomiting of pregnancy. The best method of employing it for this purpose—at least in respect to therapeutical efficiency—is in the form of suppository.[3] In an analogous state

[1] Medico-Chirurgical Transactions, vol. xlii. p. 289.

[2] ℞.—Atropiæ sulph. gr. j;
Res. podophylli, ʒj;
Ext. colocynth. comp. ʒij.
Ft. pil. no. lx.
S.—One at night.

℞.—Atropiæ sulph. gr. ½;
Magnesiæ sulph. ℥j;
Syr. limonis, f℥iij;
Aquæ, f℥v.—M.
S.—A tablespoonful before breakfast.

[3] ℞.—Atropiæ sulph. gr. ⅛;
Belladonnæ extract. gr. viij;
vel Ol. theobrom. q. s.
Ft. supposit. no. viij.

—sea sickness—atropia has been found very beneficial applied in solution to the epigastric region.[1] Dr. Le Coniat, Surgeon in the French Navy, is the author of this practice, but he does not rely upon the atropine solution alone; he conjoins with it localized electrization. It is difficult to say how far the result is due to atropia and how far to galvanism. Dr. Le Coniat affirms that the vomiting of pregnancy is equally amenable to this treatment. As my own observations show that atropia is very effective against the vomiting of pregnancy, it may be presumed that this agent is really the efficient means in the method of Dr. Le Coniat. As the local application of atropia in solution in water is capable of producing decided therapeutical results, it may be desirable to take advantage of the discovery of Dr. Waller, "who found that certain substances, such as atropia, strychnia, morphia, and the tincture of aconite when mixed with chloroform and applied on the skin, are absorbed very rapidly."[2] A solution of atropia in chloroform[3] may be applied over the epigastrium in cases of vomiting of pregnancy, or of sea sickness. I have employed the same solution externally in asthma with considerable advantage.

Atropia in Neuroses of the Pelvic Viscera.—It has been said that for pelvic pain, atropia is the best remedy. I have used it in cases of ovarian and uterine pain, in hyperæsthesia of the spermatic plexus, and in irritable bladder not dependent upon structural alteration, and the result has, in most cases, been very satisfactory. For the pain of dysmenorrhœa, the subcutaneous injection of atropia and morphia is preferable to the internal use of atropia alone.

Belladonna has long been used against that troublesome disorder—nocturnal incontinence of urine. Fuller,[4] Trousseau,[5] and various other observers report cures. Trousseau considers it the most valuable remedy which we possess against this disease (*l'arme thérapeutique la plus puissante*). In order to be successful, its full physiological influence should be steadily maintained for a considerable period. Atropia being more certain in its effects, is to be preferred to belladonna in the treatment of incontinence of

[1] New York Medical Journal, January, 1869, p. 390.

[2] Brown-Séquard, Lectures on Functional Nervous Disorders, op. cit.

[3] ℞.—Atropia, gr. ij–iv;
Chloroform. f℥j.—M.
S.—For local use.

[4] Medico-Chirurgical Transactions, vol. xlii.

[5] Clinique Médicale, tome ii. p. 659.

urine. In order to cure, it is necessary in many cases to pay attention to the state of the urinary secretion, for we find that the urine has a strong acid reaction and is loaded with uric acid. The incontinence is due in such cases to a too stimulant quality of the urine, which excites the reflex contraction of the bladder. In other cases, a mere distension of this viscus with urine having a low specific gravity causes involuntary contractions, and this condition exists during the day. This is the form of incontinence especially under the control of atropia, for this agent acts by imparting tone to the muscular wall of the bladder, and to the sphincter muscle. Indeed, as I have shown elsewhere, atropia produces a tonic contraction of the sphincter, which cannot readily be overcome by the voluntary effort in micturition. I have succeeded in the cure of nocturnal incontinence of urine by atropia, when belladonna had previously failed. In a boy of ten who had been treated by extract of belladonna, I succeeded with one-fortieth of a grain of atropia twice a day. This patient exhibited a remarkable tolerance of the remedy. Fuller ascertained a similar tolerance in the cases of his choreic patients, which he interpreted to be peculiar to that disease, but which is only a peculiarity of early life. In another place, however, he admits that this medicine acts more powerfully on adults than on children.

In involuntary nocturnal seminal emissions, a condition analogous to the preceding, atropia is a more or less valuable addition to other methods of treatment. It cannot, however, be considered a remedy sufficient in itself to cure. To produce the best effects of which it is capable, atropia must be continued for a considerable period, the constitutional effects being steadily maintained. It has seemed to me to produce decided antaphrodisiac effects.

Atropia in Affections of the Nervous System of Animal Life.— As a remedy against pain, atropia is not comparable to morphia. Messrs. Mitchell, Morehouse, and Keen affirm that atropia does not relieve pain. On the other hand, Mr. Chas. Hunter[1] believes that it possesses very great anodyne power, and for many cases of neuralgia is preferable to morphia. It is more efficacious than morphia in the cure of pelvic pain and in sciatica. It relieves and sometimes cures *tic douloureux*. In the experiments on animals detailed in another part of this paper, atropia destroyed the excitability of the sensory nerves. We cannot, therefore, refuse to admit that it

[1] Hypodermic Injections. Pamphlet, Churchill, London, 1866.

possesses pain-relieving power; but yet, my own experience has convinced me that it is much inferior to morphia. A combination of the two agents is more effective against pain than either used alone—a fortunate circumstance, since one counterbalances some of the ill effects of the other. This observation is true, at least in my experience, of the treatment of sciatica, for in a case recently under my charge, I found that the conjoined use of atropia and morphia was more effective than atropia alone.

In the treatment of pain by the use of atropia, whether administered internally or by subcutaneous injection, it is necessary to induce the full physiological effects in order to achieve the best therapeutical results. The hypodermic method is to be preferred, both in respect to certainty and permanence of effect.

In the various states of spasm, with or without pain, atropia is indicated. In convulsive *tic*, in wry neck, in the "late rigidity" which sometimes occurs in the course of hemiplegia, and in tetanus, it has been employed with more or less advantage. I have used it in these states, except tetanus, with success by hypodermic injection. Although the physiological effects of atropia indicate its employment in tetanus, the success of this practice has not been great. Physostigmia is much to be preferred in the treatment of this disease even from the point of view of its physiological effects, and clinical experience is largely in its favor.

In convulsions—epilepsy, chorea, epileptiform, hysterical, puerperal—great and immediate relief is afforded by the subcutaneous use of atropia and morphia. Belladonna is an old remedy for epilepsy. Trousseau[1] advocates its use strongly, but his recommendation of its utility is not supported by adequate statistical data, and the length of time for which it is to be used is a decided objection to its employment. For epilepsy occurring during the daytime, the convulsive seizures having the degree of severity known as the *grand mal*, no remedy probably is equal to the bromide of potassium; but for nocturnal epilepsy, for the *petit mal* and for irregular nervous manifestations, epileptoid in character, the hypodermic use of morphia and atropia, is preferable to all other means. The convulsions of children and puerperal convulsions are readily subdued by the same agents.

Dr. Fuller's experience with belladonna in the treatment of chorea, is not favorable to the use of this remedy. In a case of

[1] Clinique Médicale, op. cit.

this disease which subsequently proved fatal, I used atropia by hypodermic injection without any influence over the jactitations.

Belladonna and its active principle have been more or less used in hyperæmia of the cord and in spinal meningitis, on the suggestion of Dr. Brown-Séquard, based on the influence possessed by this remedy over the vaso-motor nerves. Although sanctioned by the authority of so great a name, I venture to oppose to this practice my personal experience of its inutility and sometimes mischievous results. Moreover, as I have ascertained, the contraction of the capillary walls produced by atropia is followed by dilatation, and after death the most constant lesion discoverable is congestion of the meninges.

Atropia in Inflammation.—In inflammatory states of other tissue than the nervous, atropia has seemed to me very beneficial. We observe in the tunics of the inflamed eye how much control atropia has over the inflammatory action. This effect—a merely local action—has, undoubtedly, its counterpart in other tissues. An attack of pleuritis or peritonitis may be cured by atropia, but preferably by the conjoint administration of atropia and morphia. When inflammatory products form, the time has passed for the use of these agents, except in the condition of great depression of the heart's action and coldness of the surface-indications for the use of atropia. Acute catarrh with profuse secretion and pharyngitis, and mercurial salivation are sometimes remarkably improved by the internal use of this agent. The action of atropia in arresting secretion of the Schneiderian mucous membrane is explained by the experiment of Prevost,[1] who has shown that ablation of the spheno-palatine ganglion is followed by profuse secretion from this membrane.

Atropia is a remedy of great value in the treatment of rheumatic inflammation. Harley has called attention to the fact that injection of atropia in the neighborhood of an affected joint will relieve remarkably the pain and inflammation. Long before this statement was published, I had been in the habit of prescribing the internal use of atropia in rheumatic affections—acute, subacute, and chronic—with marked relief to the pain and apparently diminution in the duration of the disease.

Atropia in Poisoning by Opium.—I was skeptical as to the physiological antagonism of atropia and morphia, in respect to their toxic effects, until the experience related in another part of this

[1] Journ. de Physiologie normale et pathologique. 21. 2. pp. 207–232, 1868.

paper had occurred to me. In that case every condition necessary for the solution of the problem was present. Complete insensibility, abolition of the reflex faculty, feebleness of the circulation and strong contraction of the pupil, had been produced by morphia, administered in a known quantity, and through a channel which permitted all of it to enter the blood. No other antidote was administered, and no other means of relief used, than the subcutaneous injection of atropia. Following the use of this agent, there occurred flushing of the face, warmth of the surface, return of the reflex faculty, dilatation of the pupil, more natural though profound sleep, finally restoration of consciousness, and disappearance of the narcosis. In most of the cases reported,[1] other agents and means were employed to arouse the patient. Even in Dr. S. Weir Mitchell's case (*New York Med. Journal*) electric shocks, agitation, etc., were made use of beside the belladonna, after evacuation of the contents of the stomach by the stomach pump. In a case of atropia poisoning reported by Dr. A. D. Williams,[2] of Cincinnati, morphia was alone used as the antidote, with a successful result. There can be no question, then, as to the antagonism between these two agents with respect to toxic effects. In applying this antagonism in practice, special attention should be paid to the relative duration of toxic activity, and to the proportionate quantities of one needed to overcome poisoning by the other. In my own case $\frac{1}{2\frac{1}{4}}$ of a grain of atropia was equal in respect to physiological antagonism to one grain of morphia. The effects of this dose of atropia lasted twelve hours longer than the morphia. It is to be observed, however, with regard to the quantity of atropia and morphia respectively necessary, that individuals vary as to susceptibility. Thus, in the young, morphia is more, and atropia less active than in adults. Atropia is, also, more active in blondes than in brunettes. *Cæteris paribus*, $\frac{1}{2\frac{1}{4}}$ of a grain of atropia may be considered equal to one grain of morphia. In treating narcosis produced by either agent, it is of great importance not to dilate or contract the pupil beyond the natural condition. Further, the deep somnolence produced by the two agents must not be confounded with the toxic effects of either, and the mistake be made of attempting to overcome this state of the brain by further administration of the physiological antagonist.

[1] Dr. W. F. Norris, Am. Journal of Med. Sciences, Oct. 1862. Dr. C. A. Lee, Ibid., New York Med. Journal, Nov. 1866.

[2] Lancet and Observer, Nov. 1868.

Atropia as an Agent modifying or promoting the Action of Remedies.—I have already indicated the mutual reactions which ensue when atropia is administered conjointly with certain remedies, but some additional observations are necessary on this topic.

The combination of atropia and physostigmia would be seen to be proper in cases of tetanic spasm—tetanus, hydrophobia, etc.—in which physostigmia is now employed, but my experiments show that an entirely new class of actions is developed by their conjoined administration. Atropia is not a physiological antagonist to physostigmia, except in regard to their action on the organic nervous system. It would be improper, then, to use atropia against poisoning by Calabar bean; neither should they be combined in the treatment of tetanus.

Atropia modifies but does not prevent the toxic effects of strychnia. In the treatment of disease by strychnia in which it may be desirable to have the anodyne and calmative effects of atropia, the two may be combined. I have observed good effects from this combination in old cases of paralysis accompanied by rigidity and a painful state of the skin and muscles.[1] In cases of diminished sexual power with feeble erections and imperfect action of the ejaculatory apparatus, I have also used internally the sulphate of atropia and sulphate of strychnia,[2] with marked advantage. Such a combination, is also effective in convulsive *tic*, injected into the muscles the seat of the disordered action.

I have already written at sufficient length of the modifying influence which atropia exerts upon morphia.

As an agent modifying the action of purgatives, belladonna is much to be preferred to hyoscyamus. As atropia is much more certain in its effects, it should be used rather than the belladonna. It increases the activity and diminishes the pain and griping which so commonly attend the action of resinous cathartics. Moreover, by increasing the tonicity of the muscular layer of the bowels, it diminishes the tendency to inaction which results after the use of cathartic medicines.

As the flow of urine is increased by atropia, I have used it in cases of dropsy in conjunction with other remedies. Thus, it pro-

[1] Nitrate of strychnia $\frac{1}{48}$ of a grain, atropia $\frac{1}{96}$ of a grain, used by hypodermic injection.

[2] ℞.—Atropiæ sulph. gr. j;
Strychniæ sulph. gr. ij.
Ft. pil. 100. S.—One night and morning.

motes the diuretic action of digitalis and lessens the danger of its depressing the action of the heart. It is obvious that atropia is contraindicated in cases of granular or waxy kidney. It is useful in those cases of dropsy, accompanied by asthma, in which the cardiac lesion consists of dilatation of the cavities and deficient contractile power of the walls of the heart.

CHAPTER II.

PREPARATIONS OF ATROPIA.

THE frequent references in the preceding pages to the hypodermic use of atropia, requires some further observations on the solutions to be employed. I have already indicated the quantity of atropia to be administered internally or by hypodermic injection in certain states of disease.

The requisites of a proper solution for subcutaneous injection are—

1. The solution must be neutral.
2. The solution must be perfect—*i. e.*, free from crystals, particles of dirt, etc.
3. The solution must not be too concentrated.

The sulphate of atropia is readily soluble in water. I prepare for my own use a solution containing two grains to the ounce of water, as in the following formula:—

℞.—Atropiæ sulph. gr. ij;
Aq. dest. f℥j.—M. Filter.

Five minims of this contain $\frac{1}{48}$ of a grain of atropia. If the solution be too concentrated, more irritation will result at the point of injection, than if the solution were sufficiently diluted. Moreover, if the quantity to be injected be very small, it is very difficult even with an accurate instrument to inject the exact amount intended. As no injury to the tissues is wrought by pure distilled water, there can be no objection to the use of dilute solutions.

For the relief of pain and spasm and to procure sleep, it is better to use a solution containing both morphia and atropia than either alone. I prepare a morphia solution as follows:—

℞.—Morphiæ sulph. gr. xvj;
Aquæ destil. f℥j.—M. Filter.

Seven and a half minims contain $\frac{1}{4}$ of a grain of morphia. These solutions may be combined as follows:—

℞.—Sol. morphiæ sulph. ʒvj;
Sol. atropiæ sulph. ʒij.—M. Filter.

Ten minims of this contain $\frac{1}{96}$ of a grain of atropia and one-fourth of a grain of morphia. Ten minims of the mixed solutions is a suitable quantity for ordinary purposes. The relative proportions of the atropia and morphia may be varied according to the particular indications to be met.

When a solution of atropia is kept for a few days, and sometimes for a few hours, a minute organism is developed in it—a *penicillum*. Various agents without irritant properties have been used to prevent the development of this organism hitherto, in my experience, without satisfactory results. A solution of carbolic acid—one per centum—has been tried and recommended; alcohol, alum, and some others have been patiently tested by a medical friend, without, however, as yet hitting upon a substance which itself, without having irritant qualities, may prevent the growth of this organism. So unsatisfactory have these efforts proved, that I now content myself with frequent preparation of the solution. To prepare a large amount of the solution, and frequently filter it, in order to rid it of the parasitic plant, is not proper; for we find that such solution rapidly loses strength, the growth of the organism taking place, in part at least, at the expense of the atropia.

Julius Dexter Esq.

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